Diffuse palatal swelling

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CLINICAL PRESENTATION

A 66-year-old white female presented to the Oral Medicine clinic at the Tufts University School of Dental Medicine (Boston, MA) with a 6-year history of bilateral submandibular and parotid gland swelling. She described asymptomatic swelling in the submandibular region, with intermittent increases and decreases in size, accompanied by subjective xerostomia and xerophthalmia. The patient had an empirical diagnosis of sicca syndrome and had been evaluated by the Departments of Otolaryngology and Rheumatology without resolution of her symptoms. Computed tomography (CT) examination of the submandibular gland and surrounding structures indicated swelling of the bilateral submandibular glands; the findings were suggestive of Sjögren syndrome (SS), although previous workup, including serologic markers (anti−Sjögren syndrome−related antigen A [anti-SSA], anti−Sjögren syndrome−related antigen B [anti-SSB] antibodies) and biopsy of minor salivary glands from the lower lip, did not support this diagnosis. For 3 years, the patient had been followed up by the Department of Oral Medicine, with recall examinations performed every 3 to 6 months. The initial measurement of unstimulated salivary flow rate was 0.15 mL/min. The patient's xerostomia was reasonably well controlled with prescription cevimeline 30 mg three times daily, in addition to over-the-counter sialagogues. The unstimulated salivary flow rate was significantly improved to 1.10 mL/min after treatment.

The patient's past medical history was significant for hypertension, osteopenia, and paroxysmal atrial fibrillation. Her medications included cevimeline (Evoxac), dofetilide (Tikosyn), lisinopril (Prinivil), metoprolol (Lopressor), rivaroxaban (Xarelto), artificial tears, calcium, and multivitamins. She reported an allergy to flecainide (Tambocor), and her family and social history were noncontributory.

Extraoral examination revealed nontender, firm swelling of the bilateral submandibular glands (Figure 1A) and parotid glands. Intraoral examination revealed painless, diffuse enlargement of the mucosa of the hard palate, with a boggy consistency and red-purple discoloration (Figure 1B).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for painless, firm, diffuse swelling of the palatal mucosa includes lymphomas, immune-mediated diseases, minor salivary glands tumors, and benign peripheral nerve sheath tumors.

The presentation of diffuse palatal swelling raises the consideration of non-Hodgkin lymphomas (NHLs), which are among the most common malignancies of the hard palate.[1] Diffuse large B-cell lymphoma is the most common type of NHL in the maxillofacial region; other types include follicular lymphoma and extranodal T-/natural killer (NK) cell lymphoma, nasal type.[2] Extranodal lymphoma of mucosa-associated lymphoid tissue is commonly seen in the salivary glands, especially in association with SS.[3] Intraoral NHL is often asymptomatic but may be painful or present with lymphadenopathy.[4]

Immunoglobulin G4−related disease (IgG4-RD) is a rare immune-mediated condition, first recognized as a systemic condition in 2003.[5] The disorder is characterized by multiple tumor-like swellings, a lymphoplasmacytic infiltrate with numerous IgG4-positive plasma cells, and fibrosis. Sites commonly involved include the pancreas, lungs, hepatobiliary tract, lymph nodes, and major salivary glands. The disease can mimic lymphoma, autoimmune disease, and/or inflammatory disorders. Salivary glands are one of the most common sites of IgG4-RD involvement in the head and neck region.[6] Mikulicz disease, or IgG4-related sialadenitis, characterized by xerophthalmia, xerostomia, and salivary gland enlargement, can resemble SS.[7]

Another possible diagnosis is a minor salivary gland tumor (MSGT). MSGTs represent less than 20% of all salivary gland tumors.[8] Pleomorphic adenoma is the most common benign tumor of the minor salivary glands, whereas mucoepidermoid carcinoma, adenoid cystic carcinoma, and polymorphous adenocarcinoma

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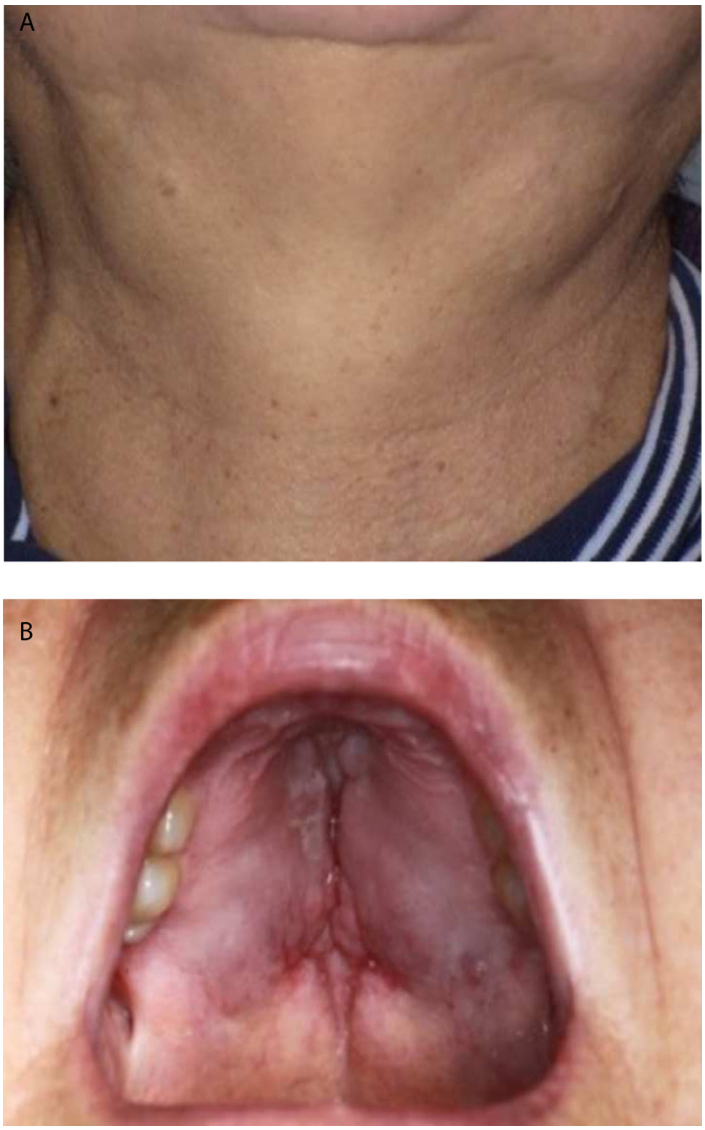


Fig. 1. **A,** Bilateral firm swellings of submandibular glands. **B,** Diffuse red-purple swelling of the mucosa of the hard palate.

are the most common malignancies.[9] MSGTs occur most frequently in women in their sixth decade and often present as asymptomatic swellings, with or without ulceration and pain.[10]

Intraoral benign peripheral nerve sheath tumors often involve the palatal mucosa and present as masses or nodules.[11] Palisaded encapsulated neuromas (solitary circumscribed neuromas), in particular, have a predilection for the oral cavity, which is the second most frequent location after skin, and the palatal mucosa is the most common intraoral subsite.[11,12] These tumors tend to present in adults (mean age 51 years) as solitary, firm, sessile swellings, which may or may not be encapsulated.[13] Unlike mucosal neuromas or neurofibromas, palisaded encapsulated neuromas are not associated with multiple endocrine neoplasia or neurofibromatosis.

DIAGNOSIS AND MANAGEMENT

An incisional biopsy of the lesion was performed, and histopathologic evaluation revealed atypical proliferation of lymphocytes and plasma cells (Figure 2). Immunohistochemical studies revealed that the lymphoid component consisted predominantly of CD20-positive B cells admixed with scattered CD3-positive T cells and numerous CD138-positive plasma cells. The results of CD5, CD23, and cyclin D1 staining were negative. On the basis of the overall findings, the diagnosis of a mature B-cell lymphoma of indeterminate phenotype and lymphoma of mucosa-associated lymphoid tissue was entertained. These initial histopathologic findings supported a diagnosis of B-cell lymphoma with plasmacytic infiltration, and the patient was referred to the Hematology-Oncology Department for further evaluation.

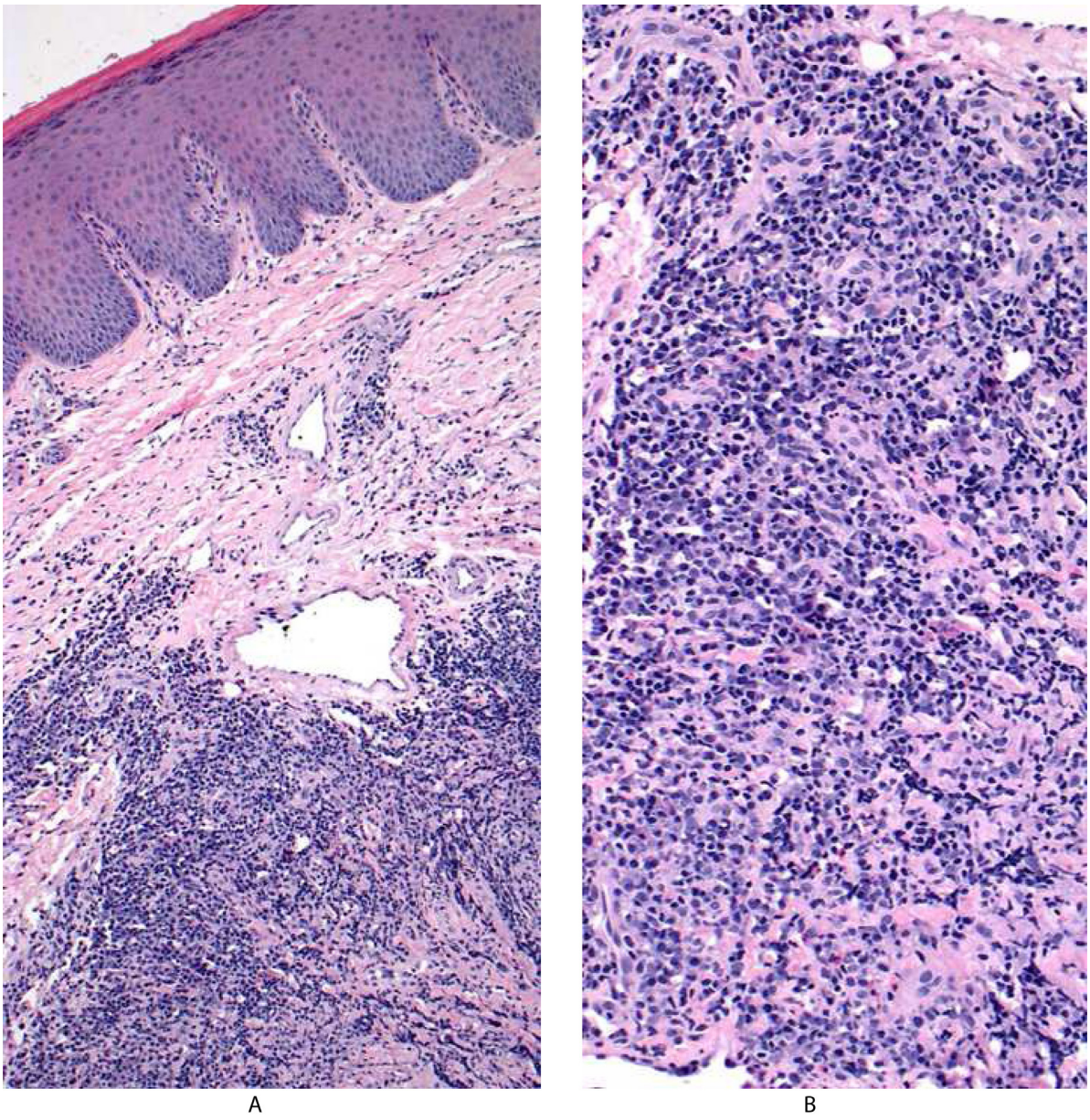


Fig. 2. Prominent subepithelial lymphoplasmacytic infiltrate with occasional eosinophils (**A,** hematoxylin and eosin [H&E], original magnification × 100; **B,** H&E, original magnification × 200). *A high-resolution version of this slide is available as eSlide:* VM05716.

Subsequent CT confirmed bilateral enlargement and nodularity of the submandibular and parotid glands with prominent bilateral cervical lymph nodes (Figure 3). Chest and abdominal CT scans showed irregular soft tissue thickening at the right upper lobe bronchus and a hypodense lesion in the neck of the pancreas. Fine-needle aspiration of the pancreatic lesion revealed fibrosis and a lymphoplasmacytic inflammatory infiltrate, and immunohistochemical studies indicated the presence of mixed population of T cells and B cells, along with polyclonal plasma cells. Additional stains for IgG4 revealed a high IgG4-to-IgG ratio, supporting the diagnosis of IgG4-related autoimmune pancreatitis. Lung biopsy findings were consistent with those of the pancreas. Serologic evaluation indicated significantly elevated serum IgG4 levels (1427 mg/dL; normal range 4−86 mg/dL). Additional immunohistochemical studies performed on the palatal specimen revealed IgG4 reactivity (Figure 4). This constellation of findings was deemed consistent with a diagnosis of IgG4-RD, and the patient was treated with a tapering course of systemic prednisone, starting at 40 mg/day, administered over 6 months.

Ten weeks after the prednisone treatment was initiated, the patient presented for follow-up, with resolution of her palatal and major salivary glandular

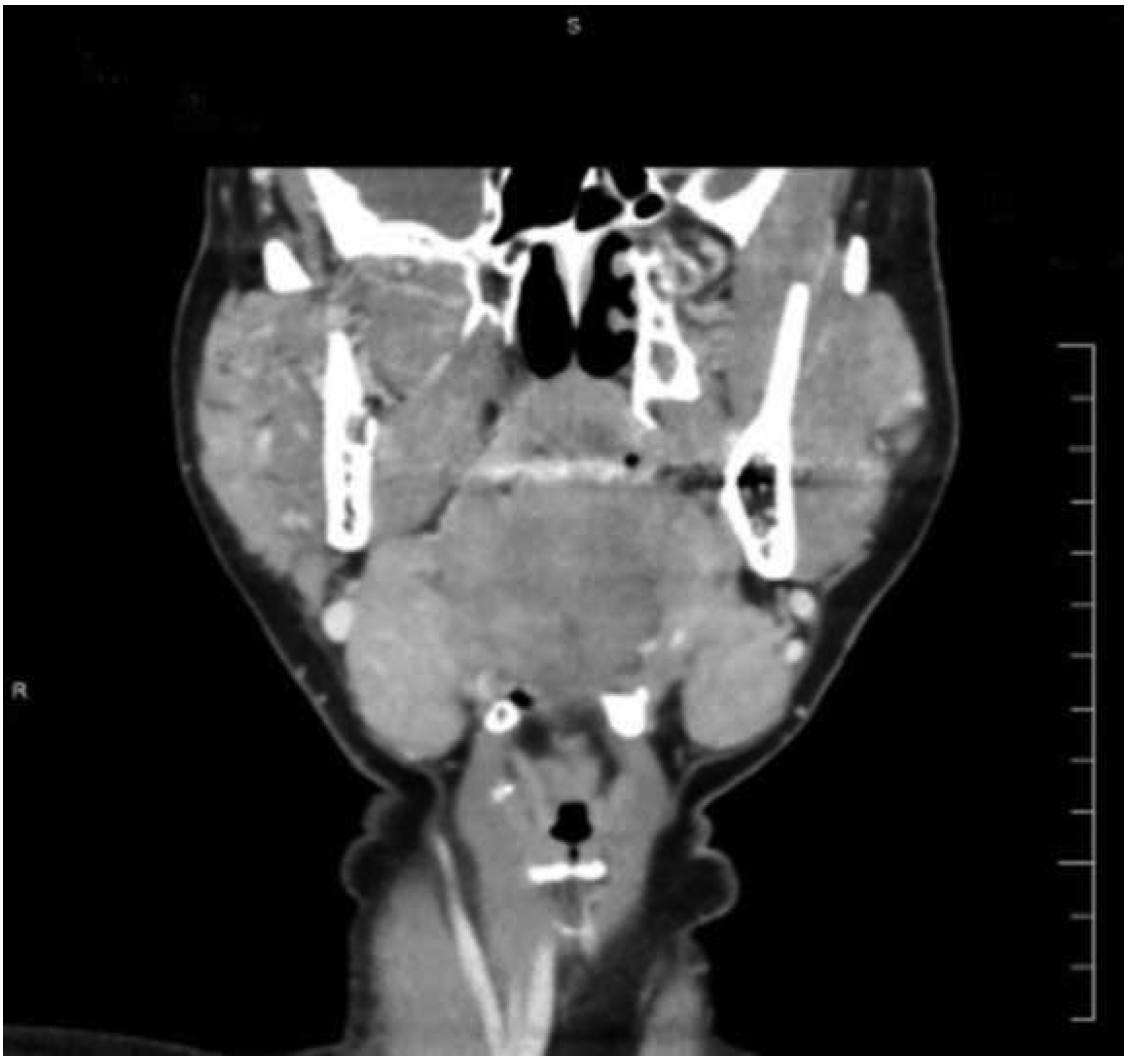
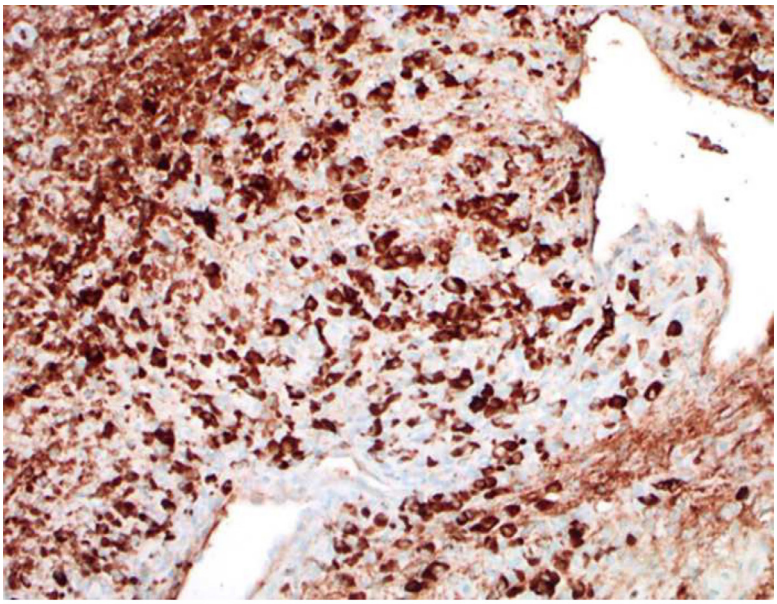


Fig. 3. Computed tomography (CT) images depicting bilateral enlargement and nodularity of the major salivary glands.

swellings (Figure 5), in addition to resolution of the pancreatic and lung lesions. There was a marked decrease in her serum IgG4 levels after 7 months of systemic prednisone treatment (298 mg/dL). The patient continues to be in remission on a daily maintenance regimen of rituximab and 7.5 mg prednisone.

DISCUSSION

IgG4-RD is a rare newly described systemic immune-mediated condition. It can affect multiple organ systems, most commonly the pancreas, salivary glands, kidney, orbit, lungs, and lymph nodes.[14] It is usually reported in males older than 50 years of age, and the incidence of IgG4-RD is approximately 0.28 to 1.08 per 100,000 individuals.[14] The disease is characterized by multiple tumefactive lesions infiltrated by IgG4 plasma cells, often with elevation of serum IgG4 levels.[5] The pathogenesis for IgG4-RD remains incompletely elucidated; however, the current understanding is that this may represent an autoimmune process, with potential antigens including galectin-3 or laminin 111.[7,15,16] Subsets of T lymphocytes also appear to play a role, with increased numbers of follicular helper T cells detected in the peripheral blood and tissue of patients with IgG4-RD.[17] Diagnosis may be challenging because many of the symptoms are nonspecific and may mimic inflammatory or neoplastic diseases, including SS and non-Hodgkin lymphoma.[18] There is no specific test for the definitive diagnosis of IgG-RD, and diagnosis is usually made on the basis of a combination of clinical symptoms, histopathology, serology, and imaging. The key histologic features of the disease include dense infiltration of the affected organ by IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and mild eosinophilic infiltration. However, the histologic presentation of IgG4-RD can mimic lymphoma, and immunohistochemistry is required to confirm diagnosis of IgG4-RD.[19] The characteristic



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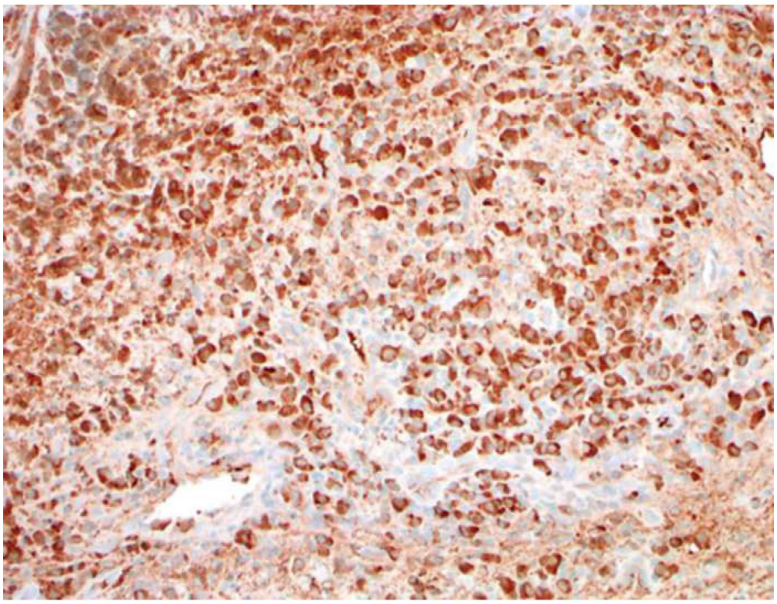

B

Fig. 4. Cells positive for immunoglobulin G (IgG) and IgG4 (**A,** immunohistochemistry, IgG; original magnification × 200; **B,** immunohistochemistry, IgG4; original magnification × 200)

histologic appearance with immunohistochemistry, which reveals greater than 30 IgG4 plasma cells per high power field and an IgG4-to-IgG plasma cell ratio greater than 50%, is highly suggestive of the diagnosis.[20] Advanced imaging can be used to detect the tumefactive lesions and may support the diagnosis. However, IgG4-RD has no specific imaging features, which vary from one organ to another.[20] Elevated serum concentrations of the IgG4 level (135 mg/dL) can suggest the diagnosis, but this is insufficient because normal levels of IgG4 have been reported in at least 20% to 40% of the patients and because elevated levels of serum IgG4 can be seen in healthy individuals.[21-23] Untreated disease can cause organ destruction and failure. Systemic corticosteroids are considered the first line of treatment, with complete remission reported in the majority of cases. Targeted immune-modulators, such as rituximab, may play a role in maintenance therapy.[24]

This case report describes a patient with bilateral salivary gland swelling managed for xerostomia, with recent onset of swelling on the mucosa of the hard palate that was initially deemed worrisome because of suspicion of extranodal non-Hodgkin lymphoma based on both its clinical and histopathologic features.

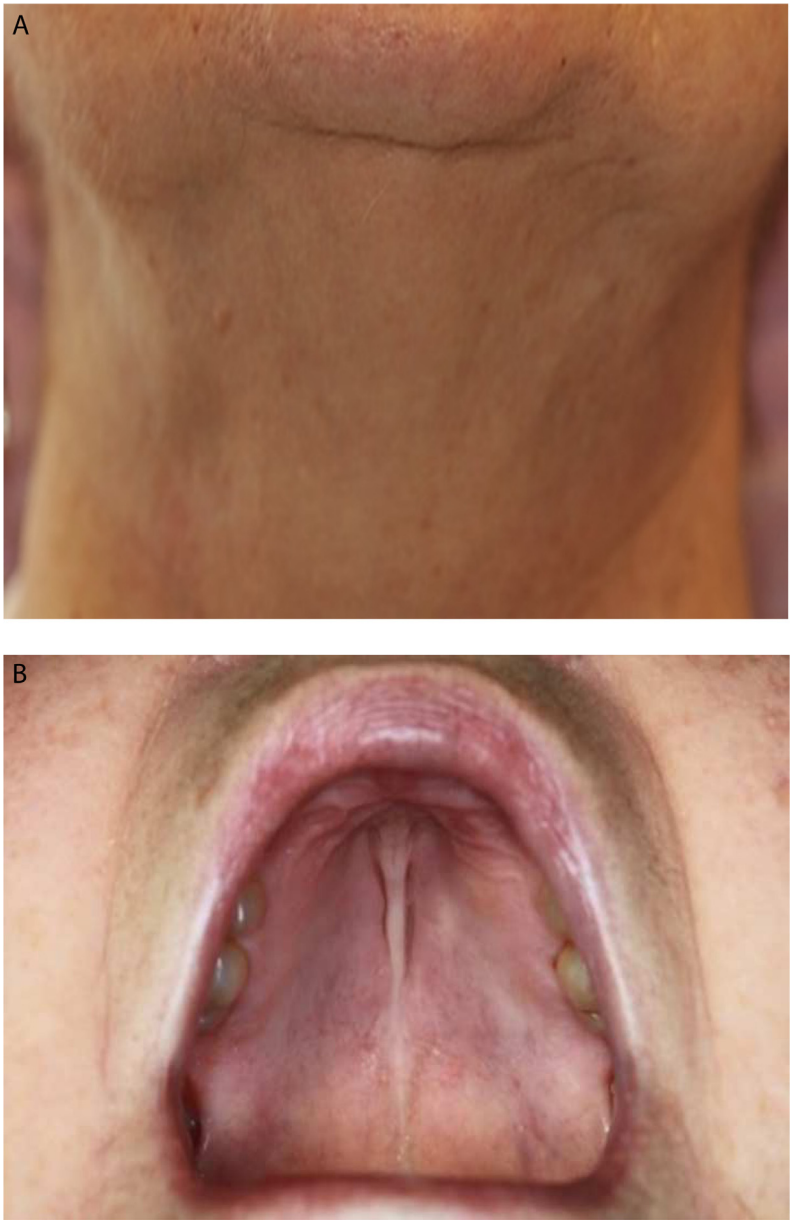

Fig. 5. Resolution of swellings of submandibular glands **(A)** and palatal mucosa **(B)** after treatment.

Comprehensive workup revealed multiorgan involvement, and a final diagnosis of IgG4-RD was made after immunohistochemical studies. A systematic review of 730 patients by Mulholland et al. found that the orbit (52.6%) is the most common site of disease in the head and neck region, followed by the salivary glands (22.2%).[25] In most cases, lesions were reported in the submandibular and parotid glands, whereas there was only 1 case of minor salivary gland involvement. This had presented as a nodular swelling of the mucosa of the hard palate bilaterally, with enlargement of the parotid and lacrimal glands.[26] The diagnosis of IgG4-RD was confirmed through histopathology, with the aid of IgG4 and IgG staining, serum IgG4 levels, and magnetic resonance imaging (MRI); that patient declined corticosteroid treatment, and the palatal lesion disappeared spontaneously after 15 months.

SS should be considered in the differential diagnosis of IgG4-RD because of the overlapping symptoms in both conditions, such as salivary gland enlargement and xerostomia.[27] The current patient had previously undergone minor salivary gland biopsy to rule out the former diagnosis without a sufficient focal score to support a diagnosis of SS. Recently, it has been reported that detection of IgG4 in the minor salivary glands aids in the diagnosis of systemic multiorgan IgG4-RD.[28] Although immunohistochemical studies to detect IgG4 are not the standard of care at present when minor salivary gland biopsies are

performed to rule out SS, the presence of multifocal swellings in other areas of the body should raise the consideration of IgG4-RD and may warrant ordering IgG4 staining, when appropriate.[14]

Clinical suspicion of IgG4-RD may arise in the presence of multiple tumefactive lesions detected clinically or through advanced imaging, and diagnosis can be aided with detection of IgG4 infiltrates in the affected sites.[29] Although IgG4-RD is an immune-mediated phenomenon, on rare occasion, it has the potential to develop into lymphoma and, therefore, is a concern that managing clinicians should be cognizant of.[30]

CONCLUSIONS

This case report highlights the complexity of an IgG4-RD diagnosis and the broad differential diagnoses, including extranodal lymphoma and SS. Oral health care providers should be familiar with this rare systemic disease when considering swellings in the head and neck region to ensure that patients receive the appropriate treatment.

PRESENTATION

An abstract describing this case was previously published following oral presentation at the annual meeting of the American Academy of Oral Medicine in San Antonio, TX, USA, in April 2018.

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